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Clinical Endocrinology (1985), **22**, 293–312

REVIEW

NEUROENDOCRINOLOGY OF MENOPAUSAL FLUSHES: AN HYPOTHESIS OF FLUSH MECHANISM

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The irreversible cessation of menses or menopause occurs at a mean age of about 51 years (Jaszman, 1976), and is the result of the depletion of ovarian follicles and the associated reduction in oestrogen secretion (Baird & Guevara, 1969). Declining plasma levels of oestrogen lead to an elevation of the pituitary gonadotropins, LH and FSH, as negative feedback is decreased (Yen & Tsai, 1971; Yen *et al.*, 1972). Dramatic pulsatile release of LH occurs at 60 to 90 min intervals (Santen & Bardin, 1973; Yen *et al.*, 1974; Casper *et al.*, 1979) while a less distinct pulsatile pattern of FSH is seen, which is probably due to the appreciably longer circulating plasma half-time of FSH (180 min) than of LH (30 min) (Yen *et al.*, 1968, 1970). Of the numerous neuroendocrine manifestations of the menopause, the most distinctive and perhaps the most distressing is the menopausal flush or hot flush. Approximately 75% of women undergoing natural menopause experience hot flushes (McKinlay & Jeffreys, 1974), while the incidence of flushes in castrate individuals may be as high as 94–100% (Erkkola *et al.*, 1973; Chakravarti *et al.*, 1977). This neuroendocrine event is unquestionably related to oestrogen withdrawal and is so characteristic as to be almost pathognomonic of ovarian failure.

PHYSICAL MANIFESTATIONS OF FLUSH EPISODES

Menopausal flushes occur with sudden onset, usually beginning with an intense feeling of heat centred on the upper body and often associated with a visible reddening of the face and neck. This feeling of heat rapidly spreads to become generalized and is accompanied by palpitations and profuse sweating. Often external methods of cooling such as fanning or disrobing are used to cope with the feeling of heat. Flushes are usually followed by a feeling of chilliness, sometimes accompanied by shivering. Hot flushes may occur infrequently or as often as hourly throughout the day and night. Those which occur during the night are invariably associated with arousal from sleep (Erlik *et al.*, 1980). If untreated, this manifestation of decreased ovarian function can go on for five years or more (Thompson *et al.*, 1973; McKinley & Jeffreys, 1974) before disappearing. Because of these intense symptoms and consequent sleep disturbance, which can occur for a long

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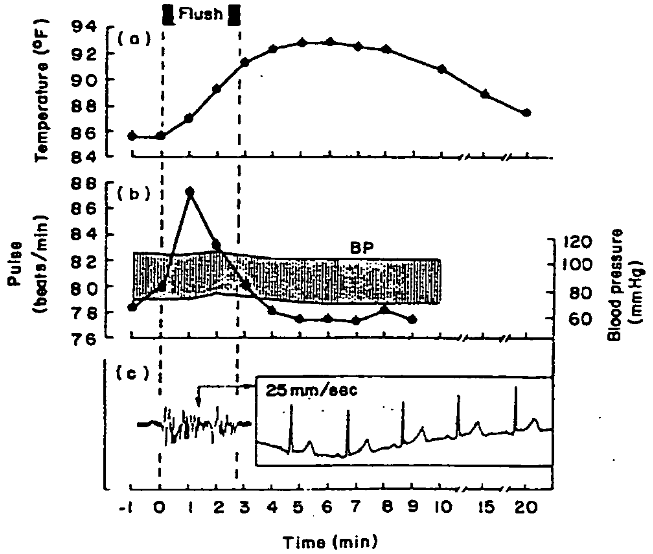

Fig. 1. Physical changes during 42 flushes monitored in six subjects. The mean (±SEM) duration of the subjective feeling of warmth (2·7±0·1 min) is indicated by the solid bar marked 'Flush'. **a**, A mean increase in finger temperature of 4·1°C (7·4° Farenheit; $P<0{\cdot}001$) is seen at 6 min and persists after the subjective feeling of warmth. **b**, Pulse rate (●) increases 9·1 beats per min ($P<0{\cdot}001$) with no associated change in blood pressure. A dramatic electrocardiogram (ECG) fluctuation during the flush is shown at a paper speed of 1 mm/s and at the normal paper speed of 25 mm/s in the inset. At the normal speed, it is apparent that the rhythm and components of the ECG are normal and fluctuation of the baseline is the cause of the unusual pattern of the tracing.

period of time, it is not surprising that the menopausal female has been described as irritable, forgetful, neurotic or depressed and that oestrogen therapy appears to improve these cognitive and affective functions (Erlik *et al.*, 1980) as well as the flush itself.

Since this clearly defined symptom complex is uniformly described by at least three-quarters of menopausal women, it seems inconceivable that many authors in the past attributed menopausal flushes to a psychogenic origin. In fact, it was not until 1974 that a systematic investigation of the physiological nature of menopausal flushes was undertaken (Molnar, 1974). Molnar carried out an elegant physiological study of hot flushes in a single subject and set the stage for a rapidly growing field of neuroendocrine research. Molnar's original observations have been confirmed by numerous investigators, including ourselves (Fig. 1). Molnar attached thermisters to many of the body surface areas which subjectively feel hot during a flush, but found no marked changes in temperature; most of these areas were also the sites of demonstrable perspiration and it is quite likely that cooling of the skin by evaporation negated any change in temperature. However, a dramatic increase in temperature was noted on the surface of the fingers and toes. In six postmenopausal women, we measured finger temperature by means of thermisters during 55 flushes (Casper *et al.*, 1979). We found an average increase in finger temperature of 4·1°C from a mean of 29·7±0·7°C (SEM) at the onset of a flush to a peak of 33·8±0·4°C ($P<0{\cdot}001$) 6 min later. Finger temperature increases as great as 7°C occurred in some subjects.

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Plethysmographic studies (Ginsburg *et al.*, 1981) have demonstrated that this increase in finger temperature is secondary to vasodilation and increased blood flow through the hand and forearm. Similarly, thermographic photography has revealed vasodilation throughout the entire upper body (Sturdee & Reece, 1979) during menopausal flushes, supporting the contention that evaporative cooling probably prevents a measureable increase in skin temperature. In our series of patients, the mean subjective duration of the flush was 2·7 ± 0·1 min although the increase in finger temperature, which begins with the onset of the feeling of heat, lasted about 20 min. Concurrent with the onset of the flush was an elevation in heart rate of 9·1 beats per min at 1 min. The heart rate returned to baseline by the end of the subjective feeling of heat. There was no flush-associated change in blood pressure. We confirmed the finding of a rapid fluctuation of the electrocardiographic baseline during the subjective flush episode, a finding which Molnar (1974) postulated was secondary to rapid changes in skin resistance caused by sweat duct opening and filling with perspiration. It has since been shown by Tataryn *et al.* (1980) that skin conductance increases (or skin resistance decreases) significantly with the onset of the flush and may be the most consistent objective parameter of the occurrence of a flush. Core body temperature has been measured during and after flushes, initially by Molnar (1974), and later by others (Tataryn *et al.*, 1980; Silverman *et al.*, 1981). It is quite clear, from these records, that internal temperature is normal at the onset of the flush but rapidly declines during and following the flush episode.

CENTRAL MECHANISM(S) FOR THE MENOPAUSAL FLUSH

From the numerous physiological investigations described above we conclude that menopausal flushes represent dysfunctional thermoregulation, initiated centrally in

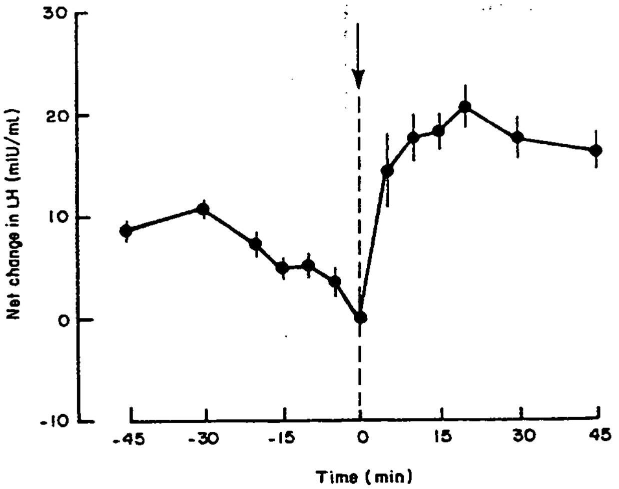

Fig. 2. Pattern of pulsatile LH release and 77 associated menopausal flush episodes. Arrows indicate flush onset. Each part illustrates a separate 8–10 h study in which blood samples were obtained at 15 min intervals. Note that each flush is synchronized with an LH pulse. Taken from Casper, Yen & Wilkes, M.M. (1979). Copyright: American Association for the Advancement of Science.

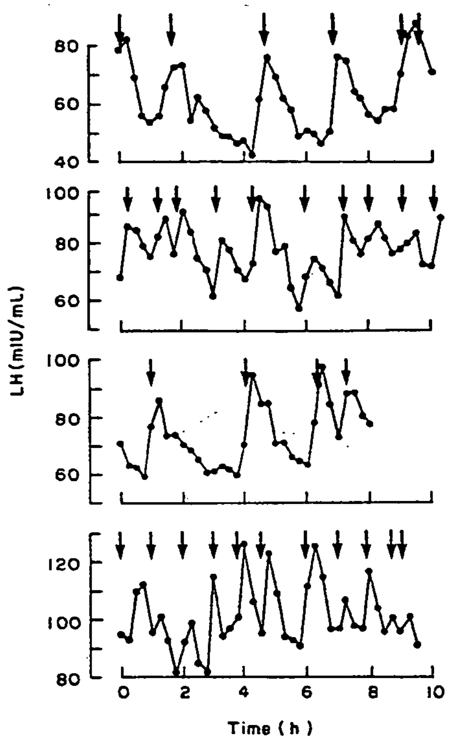

Fig. 3. Mean (±SEM) serum LH concentration during 77 flush episodes expressed as net change in mIU/ml from the onset of the flush at time 0. This graph incorporates 5 min sampling from 20 min before to 20 min after each flush episode. It can be seen that the flush onset is coincident with a rise in serum LH and all LH values after the flush are significantly elevated ($P < 0{\cdot}001$).

hypothalamic thermoregulatory nuclei. Peripheral vasodilation with profuse perspiration are potent and characteristic components of heat loss mechanisms (Proppe & Gale, 1970; Smiles *et al.*, 1976), and during menopausal flushes these heat loss mechanisms are inappropriately activated in the presence of normal core body temperature. The rapid loss of body heat during and immediately after a flush is followed by shivering, a mechanism by which the body raises core temperature back toward normal (Gale, 1973). Exposure to cold appears to override the inappropriate heat-loss mechanisms during flushes. Both subjective and objectively measured flushes stopped immediately in two subjects with frequent menopausal flushes, when they were placed in a room at 4°C (R. F. Casper & S. S. C. Yen, unpublished observation). This finding is consistent with the reports of a significant positive correlation between the mean number of flushes per day and the ambient temperature (Coope *et al.*, 1978; Molnar, 1981). Thus normal thermoregulatory mechanisms seem to predominate in a cold environment to prevent a possibly dangerous loss of body heat.

Further support for a central mechanism of menopausal flushes has been obtained from hormonal measurements during flush episodes. Several reports attempt to

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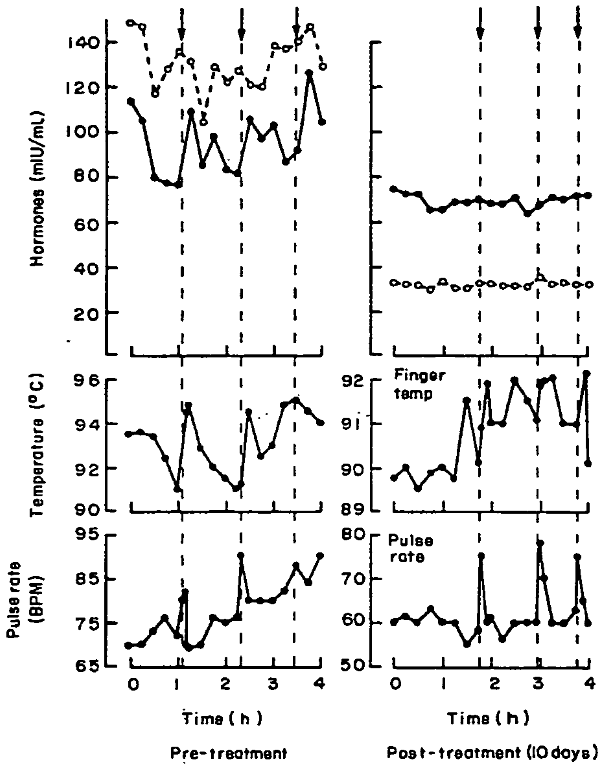

Fig. 4. Finger temperature in degrees Fahrenheit (°F) and pulse rate in beats per min (BPM) associated with flush episodes (arrows) and serum concentrations of LH (●) and FSH (○) in mIU/l in a hypogonadal subject before and after 10 d of daily LRF agonist administration (50 μg subcutaneously). After 10 d of LRF agonist treatment, LH and FSH levels are decreased and LH pulses are absent. However, subjective flushes still occur and these are documented objectively by an increase in finger temperature and pulse rate coincident with each flush. Taken from Casper & Yen (1981). Copyright: Endocrine Society.

demonstrate a correlation between hot flushes and the circulating levels of oestrogens and gonadotropins in menopausal women (Aksel *et al.*, 1976; Abe *et al.*, 1977; Chakravarti *et al.*, 1977; Hutton *et al.*, 1976). All of these studies, based on daily or less frequent sampling, were unsuccessful in demonstrating any correlation between either oestrogen or gonadotropin levels and the incidence of flushes in hypogonadal women. However, using frequent blood sampling, as often as every 2 min in women having frequent menopausal flushes, Casper *et al.* (1979) and Tataryn *et al.* (1979) were able to demonstrate a close temporal association between menopausal flushes and pulsatile release of LH (Fig. 2). We found that menopausal flushes were invariably associated with LH pulses with the onset of the flush being coincident (Fig. 3). However, not every LH pulse which occurred in these women was accompanied by a hot flush. By downregulating pituitary gonadotropin release with a potent GnRH agonist, we demonstrated that the release of LH itself does not cause the hot flush episode (Casper & Yen, 1981).

Menopausal flushes were subjectively and objectively documented despite low LH levels and the complete absence of LH pulses (Fig. 4). DeFazio *et al.* (1983) have documented hot flushes in premenopausal women following the same regimen of GnRH-agonist treatment. Similarly, menopausal flushes have been described in women following complete hypophysectomy for pituitary tumours and with subsequent low gonadotropin levels (Mulley *et al.*, 1977; Meldrum *et al.*, 1981). Finally, the increase in LH levels which occurs following administration of GnRH-agonist does not provoke flushes (Menon *et al.*, 1983). These data suggest that pulsatile release of hypothalamic GnRH (Carmel *et al.*, 1976; Neill *et al.*, 1977) which initiates pituitary LH pulses, rather than LH itself, may be more directly associated with the dysfunction of thermoregulation during flushes. Taken together, all the available evidence suggests that menopausal flushes have a central origin involving neuroendocrine changes within the hypothalamus. The findings to date focus attention on the medial preoptic area, which is the major thermoregulatory nucleus in mammals (Adair, 1977; Gilbert & Blatteis, 1977) including man (Benzinger, 1969). This area also has high concentrations of oestrogen progesterone receptors (Kato, 1978; Pfaff & McEwen, 1983) suggesting that medial preoptic area neurons may be responsive to oestrogen sensitization and withdrawal.

While the precise mechanism remains elusive, menopausal hot flushes are independent of the ageing processes (Yen, 1977). It is established that oestrogen withdrawal, such as bilateral ovariectomy in premenopausal women and orchiectomy in testicular feminization syndrome, triggers a chain of events in the estrogen-sensitive neurons with the rapid onset (within 72 h) of symptoms of hot flushes. These target neurons appear to be endowed with cellular capacity to respond to oestrogen signal (Pfaff & McEwen, 1983) the expression of which is dependent upon prior oestrogen exposure. Thus, we have observed that in six patients with gonadal dysgenesis, even in advanced age (52), who have never been exposed to endogenous or exogenous oestrogen or progestins, menopausal flushes do not exist. However, upon withdrawal of oestrogen replacement of several months duration, all patients experienced classical hot flushes for the first time (S. S. C. Yen *et al.* unpublished observation).

POSSIBLE HYPOTHALAMIC MEDIATORS OF THE FLUSH MECHANISM

GnRH

The demonstration that LH pulses and menopausal flushes are synchronous but that LH itself does not initiate the flush mechanism, has focused attention on the hypothalamus as the site of the initiation of menopausal flushes. Reports of GnRH immunoreactive perikarya in the primate arcuate nucleus (Barry & Carette, 1975; Barry, 1977; Silverman *et al.*, 1977) have not been confirmed in more recent studies by Goldsmith and his colleagues in yellow baboons (Marshall & Goldsmith, 1980; Goldsmith *et al.*, 1983). These investigators have demonstrated that GnRH cell bodies are more numerous in the infundibular lip with the projection of short axons into the infundibulum and median eminence itself. However, of more immediate interest is the demonstration by this group of investigators that the majority of GnRH immunoreactive perikarya in primates are located in the medial septal-preoptic area. Goldsmith *et al.* (1983) have demonstrated intrahypothalamic GnRH axons arising anteriorly from medial preoptic area cell bodies and terminating in the infundibulum and median eminence suggesting that primates have a preopticoinfundibular GnRH tract. This finding suggests a possible mechanism by which activation of GnRH neurons in the medial preoptic area may result in alterations in thermoregulation synthronous with the release of GnRH. Contacts with nearby neurons were most plentiful in the medial preoptic area with up to 20 short processes demonstrated between nearby parallel bipolar neurons. Since GnRH itself has been demonstrated to inhibit electrical activity of hypothalamic neurons (Dyer & Dyball, 1974; Renaud *et al.*, 1975) these intercellular contacts could provide a mechanism for simultaneous GnRH release and themoregulatory changes. Evidence against this speculation is provided by the work of Gambone *et al.* (1982) in subjects with isolated gonadotropin deficiency, in whom GnRH synthesis and/or release is defective (DeMorsier & Gauthier, 1963). These patients experience hot flushes following oestrogen withdrawal, suggesting that GnRH may not be the mediator of menopausal flushes. However, the role of GnRH in the flush mechanism itself cannot be completely ruled out since GnRH cell bodies may still be present in the medial preoptic area with the anatomical changes of the condition precluding delivery of GnRH to the median eminence to affect LH release. Alternatively, intrahypothalamic neurotransmitters may affect both GnRH release and thermoregulation simultaneously through neuronal contacts in the medial preoptic area. Gambone *et al.* (1982) studied women with severe hypothalamic chronic anovulation. In these women, abnormal neurotransmitter activity is thought to result in reduced release of GnRH from the hypothalamus resulting decreased or absent pulsatile release of gonadotropins (Yen *et al.*, 1973) and consequent amenorrhea, hypogonadism and hypo-oestrogenism equivalent to that seen after castration. Despite oestrogen withdrawal in these patients, no menopausal flushes were recorded (Gambone *et al.*, 1982). These subjects also have evidence of increased dopamine and opioid peptide activity in the hypothalamus (Quigley *et al.*, 1980a). Taken together, these findings suggest that hypothalamic factors responsible for GnRH release, and not GnRH itself, may be responsible for the neuroendocrine changes seen during menopausal flushes. The observation that catecholamines, especially norepinephrine and neuromodulators such as the endogenous opioid peptides, play a role in the central regulation of both thermoregulation and GnRH release suggests the possibility of an adrenergic/opiate mechanism of menopausal flushes.

Norepinephrine

The medial preoptic area is innervated by ascending noradrenergic neurons from the lateral tegmental norepinephrine system and locus coerulus in the brain stem (Moore & Bloom, 1979). Thus a possible mediator of both GnRH release and thermoregulatory changes during menopausal flushes is the catecholamine system, more specifically, the noradrenergic system. Although it is necessary to extrapolate from animal data, there is evidence for this hypothesis. Increased noradrenergic activity is associated with GnRH, and subsequent LH release in rats (Sawyer, 1979; Barraclough & Wise, 1982) while in both rats and primates, alpha adrenergic antagonists (but not beta adrenergic antagonists) abolish LH pulsatile release (Bhattacharya *et al.*, 1972; Weick, 1978). Monoamines, especially norepinephrine, have also been shown to play an important role in the control of thermoregulation. Noradrenergic stimulation of the medial preoptic area in monkeys (Myers & Yaksh, 1969) and baboons (Toivola & Gale, 1970) by microiontophoretic application of norepinephrine causes peripheral vasodilation and heat loss and a drop in core body temperature similar to changes which occur in women during hot flushes. However, bradycardia and hypotension also occur in these animals indicating that adrenergic activation alone, at least in a single hypothalamic area, does not produce a picture completely analogous to menopausal flushes.

The evidence that gonadal steroids modulate central noradrenergic activity is compelling. Using autoradiography and immunohistochemistry Sar & Stumpf (1981) demonstrated oestradiol receptors in central noradrenergic neurons in the lower brainstem of the rat. Recently, using similar techniques, Sar (1984) localized E_2 binding sites to tyrosine hydroxylase-containing neurons in the hypothalamus. These findings suggest that E_2 levels may modulate catecholamine activity and synthesis in the brain. Castration in rats is associated with an increase in hypothalamic norepinephrine turnover (Anton-Tay & Wurtman, 1968; Bapna *et al.*, 1971) as well as an increase in the concentration of tyrosine hydroxylase (Beattie *et al.*, 1972). Hypothalamic levels of norepinephrine increase and those of dopamine decrease by the tenth day following castration in rats (Donoso *et al.*, 1967). Similarly, in sheep, M. M. Wilkes and S. S. C. Yen (unpublished data) have demonstrated that castration is associated with an increase in a carotid arterial-venous difference for norepinephrine within one week. In contrast, oestrogen replacement in castrated rats increases dopaminergic activity in the median eminence and decreases noradrenergic turnover (Fuxe *et al.*, 1977). In women, plasma and urine catecholamine levels vary during the menstrual cycle (Goldstein *et al.* 1983). These data indicate that castration is associated with an increased ratio of norepinephrine/dopamine in the animal brain.

Noradrenergic system and menopausal flushes

Clinical data on α-adrenergic activity is difficult to obtain, for obvious reasons. Attempts to delineate the role played by the noradrenergic system on LH pulses in humans have so far been unsuccessful (Yen *et al.*, 1972; Santen & Bardin, 1973; Yen *et al.*, 1974). Cardiovascular side-effects preclude the human use of doses of alpha adrenergic antagonists comparable to those used in the Rhesus monkey. Although we have demonstrated that peripheral circulating levels of plasma catecholamines do not change before or during flush episodes in women (Casper *et al.*, 1979), it is possible that alterations in central catecholamine activity do occur. There is evidence that both alpha methyldopa (Nesheim & Saetre, 1981) and clonidine (Clayden *et al.*, 1974; Schindler *et al.*, 1979; Edington *et al.*, 1980), two alpha adrenergic agonists which decrease noradrenergic activity centrally in the human (Van Zwietan, 1977; Reid *et al.*, 1977a), may have a beneficial effect on menopausal flushes by decreasing their frequency and intensity. Data from a double blind cross-over study comparing clonidine with a placebo after an initial treatment-free week (Clayden *et al.*, 1974) are presented in Fig. 5. At the end of the first four weeks of treatment, clonidine reduced the frequency of flushes by 44% compared to 33% for the placebo. With crossover from clonidine to placebo, there was an increase in the number of flushes but not back to baseline and at the end of the eighth week of treatment those patients receiving a placebo had maintained a 30% reduction in flushes compared to the initial treatment-free week. On the other hand, with the crossover from placebo to clonidine, there was a further decrease in the number of flushes with a 56% reduction from baseline by the eighth week of treatment. For both groups of patients, clonidine treatment was significantly better in reducing flush episodes than the placebo (clonidine before placebo, $P<0{\cdot}05$; clonidine after placebo, $P<0{\cdot}001$). Both clonidine

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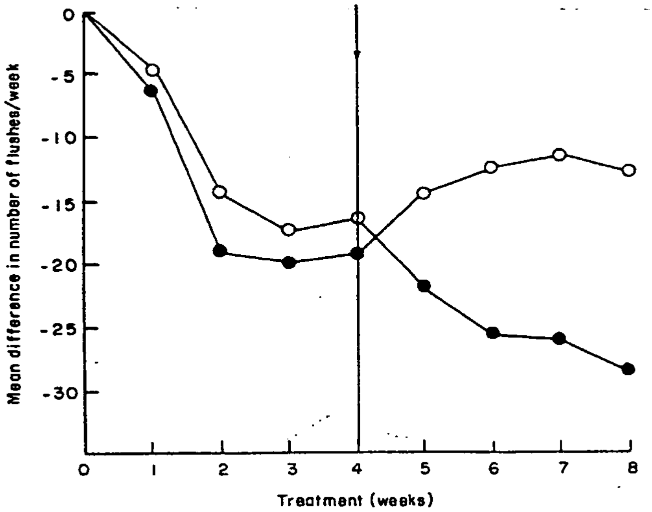

Fig. 5. Mean change in number of flushes per week from initial values during a treatment-free week. Clonidine treatment (●; $n=42$); placebo treatment (○; $n=43$). A group of subjects receiving clonidine as first treatment had a mean number of flushes of 41·1 during the treatment-free week and those subjects receiving placebo first had 50·2 flushes during the treatment-free week. Vertical line shows crossover. Taken from Clayden *et al.* (1974).

and placebo have a gradual onset of action which results in a maximal reduction of flushes after about two or three weeks. The beneficial placebo effect appears to be longlasting with a maintenance of a 30% reduction in flushes at eight weeks. It would thus appear that both clonidine and placebo may be acting through a similar mechanism to reduce the frequency of menopausal flushes. This paper, besides reinforcing the importance of the placebo effect on menopausal flushes, provides insight into the possible mechanism of flushes.

Endogenous opioid peptides and the placebo effect

The actions of both placebo and clonidine may be mediated by endogenous opioid peptides. Evidence for opioid mediation of the placebo effect is indirect. Levine *et al.* (1978) demonstrated that the analgesic effect of a placebo in dental pain is reversed by administration of naloxone, a narcotic antagonist. For clonidine and alpha methyldopa, both alpha adrenergic agonists with central effects, a large body of evidence exists implicating the mediating or modulating effects on endogenous opioid peptides. Clinically, clonidine administration to opiate addicts produces dramatic disappearance of narcotic withdrawal symptoms (Gold *et al.*, 1978a, b) while acute withdrawal of clonidine itself, in hypertensive patients, results in a symptom complex resembling narcotic withdrawal (Hunyor *et al.*, 1973; Reid *et al.*, 1977b). Clonidine has also been shown to have analgesic effects in mice (Schmitt *et al.*, 1974; Fielding *et al.*, 1978) and to attenuate the adrenergic hyperactivity seen in opiate withdrawal in rats (Aghajanian, 1978; Laverty & Roth, 1980). In spontaneously hypertensive rats, the hypotensive effect of clonidine and alpha methyldopa is blocked by naloxone (Farsang & Kunos, 1979). In a subsequent study clonidine and alpha methylnoradrenaline were found to increase the production of beta endorphin-like substance from slices of rodent brainstem (Kunos *et al.*, 1981) while clonidine has been shown to increase serum beta-endorphin levels in the rat (Pettibone & Mueller, 1981).

The role of endogenous opioid peptides in menopausal flushes

Endogenous opioid peptides are found in high concentrations in the medial preoptic area (Dupont *et al.*, 1980), while the arcuate nucleus-median eminence area contains the highest concentration of beta endorphin in the brain (Wilkes *et al.*, 1980). It is not surprising, therefore, that endogenous opioid peptides have been shown to influence both GnRH release and thermoregulation, generally opposing the actions of norepinephrine, i.e. opioid administration results in inhibition of LH pulsatile release (Sylvester *et al.*, 1980; Kinoshita *et al.*, 1980; Grossman *et al.*, 1981; Reid *et al.*, 1981) and induce hyperthermia (Clark & Ponder, 1980; Francesconi & Mager, 1981) respectively. Such changes are probably the result of a neuromodulatory effect since morphine and other opiates inhibit the activity of noradrenergic neurons (Korf *et al.*, 1974; Bird & Kuhan, 1977) and decrease neuronal norepinephrine release (Arbilla & Langer, 1978; Kalra & Simpkins, 1981).

Do endogenous opioid peptides play a role in the mechanism of menopausal flushes? As pointed out by Crawford (1977) in his article 'Hot flushes and cold turkey', oestrogen withdrawal and opiate withdrawal syndromes have many similarities. The symptoms and signs of narcotic withdrawal include hot flushes, often with visible flushing of the face and neck, perspiration, gooseflesh and shivering (cold flashes) and sleep disturbances such as insomnia and intermittent awakening (Himmelsbach, 1971; Gold *et al.*, 1978b), all of which occur with oestrogen withdrawal. Other changes occur in narcotic withdrawal which are not seen in women with menopausal flushes. However, it is likely that systemic administration of high doses of narcotics in addicts affects numerous brain and brainstem centers leading to a myriad of withdrawal symptoms. In women with menopausal flushes, it is possible that withdrawal of endogenous opioid peptides from specific hypothalamic regions is responsible for a limited withdrawal syndrome manifested by thermoregulatory and GnRH changes alone. An opiate withdrawal mechanism is also consistent with the occurrence of hot flushes in men following orchidectomy (Ginsburg & O'Reilly, 1983; Eaton & McGuire, 1983), since opioid peptides have been demonstrated to participate in the negative feedback control of LH by testosterone (Cicero *et al.*, 1979; Kinoshita *et al.*, 1980; VanVugt *et al.*, 1982; Delitala *et al.*, 1981; Moult *et al.*, 1981). DeFazio *et al.* (1984) have convincingly demonstrated that an 8-hour infusion of naloxone had no effect on the incidence of menopausal flushes in 16 symptomatic postmenopausal women, although one conflicting report exists (Lightman *et al.*, 1981a). We have also found no improvement in menopausal flushes during naloxone infusion (R. F. Casper & S. S. C. Yen, unpublished observation). These findings suggest that endogenous opioid peptides do not play a role in the initiation of flush episodes but the data are consistent with an opiate-withdrawal hypothesis.

Other clinical evidence for the possible involvement of endogenous opioid peptides in menopausal flushes is obtained in patients with pituitary prolactin-secreting microadenomas. These patients experience oestrogen withdrawal to postmenopausal levels, but do not have hot flushes. Endogenous opioid peptides are probably elevated in these

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women and contribute to their hypogonadotropinism and amenorrhea as evidenced by a rise in serum LH levels following infusion of naloxone (Quigley *et al.*, 1980b).

Corticotrophin-releasing hormone

The hypothalamic and extrahypothalamic distribution of the corticotrophin releasing hormone (CRF) neuronal system has been studied in detail. The CRF pathway that controls the pituitary ACTH secretion originates in the paraventricular nucleus (PVN) and terminates in the median eminence. The concentration of CRF in the portal blood of the rat approximates 10^{-10} md/l which is in the range that induces ACTH and β-endorphin release from adenohypophyseal tissue *in vitro* (Gibbs & Vale, 1982). The finding of CRF within the PVN has opened a new dimension of functional interaction between CRF, oxytocin and vasopressin. The PVN contains more CRF cells than either oxytocinergic or vasopressinergic cells. Furthermore, paraventriculo-autonomic projections (brainstem and spinal cord) for oxytocin and vasopressin as well as for CRF have been described (Vandesande *et al.*, 1977; Swanson *et al.*, 1983). Thus, the PVN has emerged as a potential site for integrating autonomic and neuroendocrine responses as in stress.

The adenohypophysis is of course the principle target of CRF. The initial step of CRF action on the adenohypophyseal cells involves binding of the CRF to high affinity membrane receptors. This is followed by an increase in intracellular cAMP and finally calcium dependent ACTH secretion (Vale *et al.*, 1984). Prolonged exposure to CRF stimulates the synthesis as well as the release of ACTH and related proopiomelanocortin (POMC) products. Levels of POMC mRNA are elevated by CRF. Pretreatment with glucocorticoid inhibits the CRF-mediated increase in intracellular cAMP and results in lower ACTH and POMC mRNA levels. Thus, CRF induces synthesis and secretion of POMC peptides by pituitary cells, and glucocorticoids inhibit these CRF actions directly (Vale *et al.*, 1984).

Genazzani *et al.* (1984) reported that plasma levels of ACTH, β-endorphin, β-LPH and cortisol were elevated during flush episodes. The time course of increments for these pituitary peptides were similar and concomitant with those of LH pulses but the magnitude of rise was greater. These observations are consistent with earlier findings of elevated cortisol, androstenedione and dehydroepiandrosterone in association with flushes (Meldrum *et al.*, 1980). Thus, the activation of hypothalamic CRF release may be involved in the neuroendocrine event of hot flushes. CRF may act within the brain to stimulate noradrenergic activity via the paraventriculo-automatic projection (Swanson *et al.*, 1983; Vale *et al.*, 1984), and consequently noradrenergic-mediated changes in thermoregulation and GnRH release at the anterior medial preoptic area may occur. Further, norepinephrine may also be delivered to the portal system where it potentiates the potency of CRF on the release of POMC peptides (Vale *et al.*, 1984). It is possible, however, that the activation of CRF release may represent the central response to stress secondary to the flush.

Modulation by oestrogen and progesterone

There is evidence in the human that ovarian steroid levels alter endogenous opioid peptide activity. During the menstrual cycle in normal women, naloxone administration in the late follicular or luteal phase, but not in the early follicular phase, results in increased pulsatile release of LH (Quigley & Yen, 1980; Blankstein *et al.*, 1981; Lightman *et al.*, 1981b; Ropert *et al.*, 1981) suggesting hypothalamic opioid inhibitory activity associated with elevated steroid levels. Postmenopausal or castrated women have significantly lower plasma beta lipotropin and beta endorphin levels than cycling women (Genazzani *et al.*, 1981) although there is no difference in plasma ACTH or cortisol levels. There is also evidence that endogenous opioid peptide activity is very low in postmenopausal women. Reid *et al.* (1983) demonstrated that administration of beta-endorphin or infusion of naloxone had no effect on LH levels in postmenopausal women. Similarly, infusion of naloxone by De Fazio *et al.* (1984) had no effect on the frequency or amplitude of LH or FSH pulses in hypogonadal women suggesting a very low or absent influence of hypothalamic opiates on GnRH secretion in these subjects. These findings are consistent with the disappearance of opiatergic control of LH secretion in rats following castration (Bhanot & Wilkinson, 1983) and with the undetectable levels of beta-endorphin in hypophyseal portal blood of ovariectomized monkeys (Wehrenberg *et al.*, 1982). Wardlaw *et al.* (1982) recently found that oestrogen replacement resulted in a partial return toward normal of beta-endorphin levels in these castrated monkeys, while treatment with oestrogen and progesterone resulted in complete return of beta-endorphin to precastration levels.

Several investigators have reported the effectiveness of progestins alone in the reduction of flush episodes (Appleby, 1962; Bullock *et al.*, 1975; Erlik *et al.*, 1981; Nordin *et al.*, 1980; Paterson, 1982; Schiff *et al.*, 1980; Cetel & Yen, 1984). The double-blind crossover study by Schiff *et al.* (1980) provides the definitive answer as to its effectiveness (Fig. 6). That progestins do act at a hypothalamic site is indicated by the marked reduction in amplitude of LH and FSH pulses, elevation of basal body temperature and abolition of flush episodes for the duration of the study (Fig. 7).

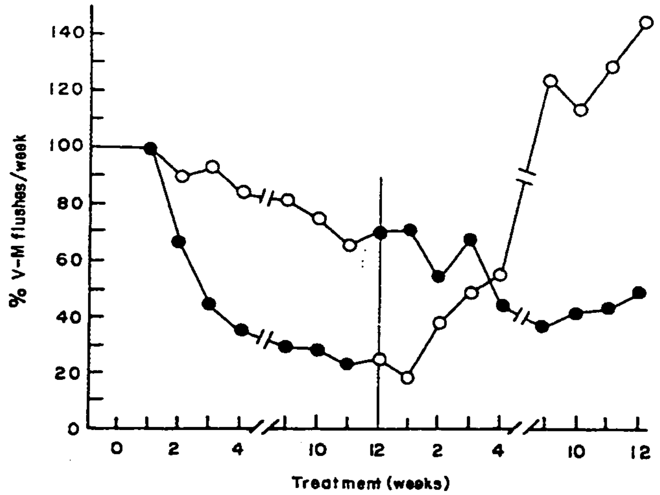

Fig. 6. Mean number of vasomotor flushes as a percentage change from pretreatment (week − 1 to 0). Change of treatment regimen (crossover, shown by vertical line) occurred at 12 weeks. Weeks 5 to 8, unassociated with major variability, are not included. Placebo (○); drug (●). (Redrawn with permission from Schiff *et al.* (1980) copyright: 1980, American Medical Association.)

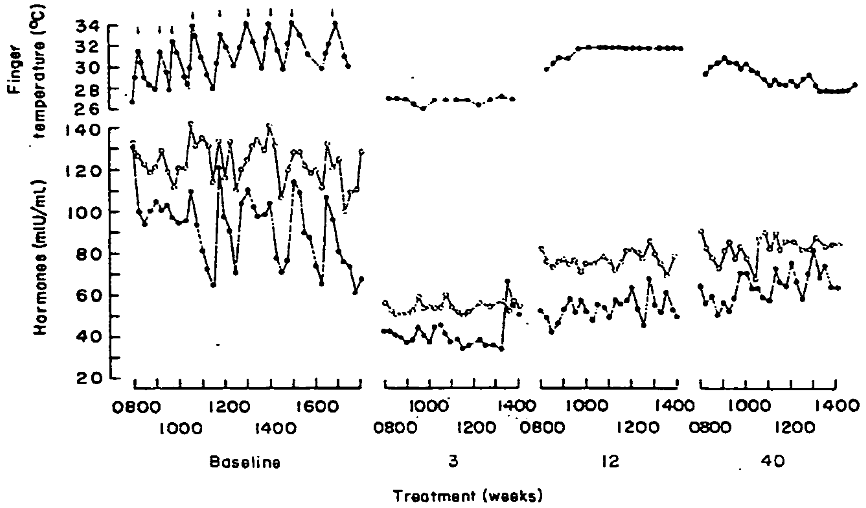

Fig. 7. The effects of a progestogen, megestrol acetate, upon centrally-mediated pulsatile gonadotrophin release, flush episodes and basal body temperature in a postmenopausal women during one year of treatment. LH (●); FSH (○). Arrows indicate flush episodes. Cetel & Yen, (1985).

We have demonstrated increased endogenous opioid peptide activity in oestrogen-deficient postmenopausal women treated with the oral progestin medroxyprogesterone acetate alone for 30 days, suggesting that the beneficial effect of progestin on hot flushes may be mediated by an opiate mechanism (unpublished data).

Other neuropeptides and temperature control

Several observations now support a neurotransmitter or neuromodulator role for a number of hypothalamic peptide hormones. In particular thyrotropin-releasing factor, bombesin, met-enkephalin, neurotensin, angiotensin II and somatostatin have been demonstrated to have direct thermoregulatory effects in animals (Morley *et al.*, 1982; Brown, 1981; Brown *et al.*, 1981; Lin *et al.*, 1980; Francesconi & Mager, 1981). The thermoregulatory actions of these peptides are varied, and complex interactions occur between peptides at differing ambient temperatures. Much more research is necessary to determine the degree to which any of these peptides influence the physiologic changes seen during menopausal flushes.

OPIATE-ADRENERGIC INTERACTION: A HYPOTHESIS FOR THE MECHANISM OF THE HOT FLUSH

The data currently available suggest a plausible hypothesis for the mechanism of the hot flush. Throughout reproductive life, physiological levels of oestrogen and progesterone maintain endogenous opioid peptide concentrations in the hypothalamus and brainstem.

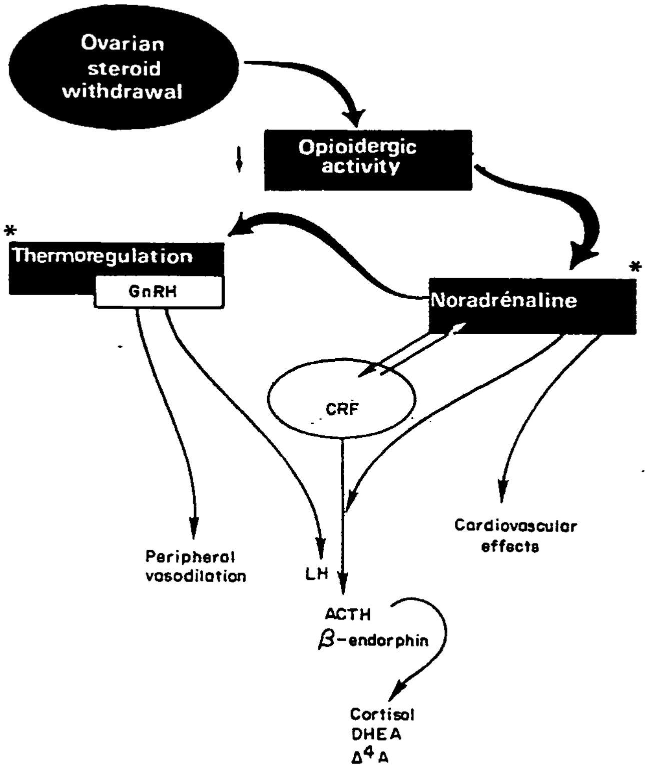

Fig. 8. A diagrammatic scheme for the proposed neuroendocrine mechanism of menopausal hot flushes. Oestrogen withdrawal induces a decrease in the inhibitory action of the hypothalamic opioidergic activity on noradrenergic neurons in the brainstem, and consequently hyperactivity of the noradrenergic inputs to the medial preoptic area, where thermoregulation and GnRH secretion are stimulated, results in peripheral vasodilation and pulsatile LH release. The increased noradrenergic activity may also account for the increased pulse rate. Activation of the CRF-POMS system may either be a component of the flush mechanism or a response to the discomfort—a central stress. *Oestrogen binding site.

Declining oestrogen levels at the time of menopause result in a decrease in endogenous opioid peptide activity with the release of noradrenergic activity from its usual tonic inhibition. Noradrenergic hyperactivity leads to a situation analogous to narcotic withdrawal. Inappropriate noradrenergic activation of medial preoptic area heat-loss mechanisms results in hot flushes which are coincident with GnRH release because GnRH cell bodies are in close proximity to, or in contact with, thermoregulatory neurons. Successful therapy for menopausal flushes such as oestrogen replacement, high dose progestin treatment, clonidine or alpha-methyldopa and placebo administration may stop flushes by increasing endogenous opioid peptide activity with consequent inhibition of noradrenergic activity below the threshold needed to activate heat loss. However, the most compelling evidence for the involvement of opioid peptides in menopausal flushes is the recent development of a possible animal model of flushes. Simpkins *et al.* (1983)

demonstrated that administration of naloxone to morphine-dependent rats resulted in intermittent surges in tail-skin temperature which were linked to LH pulsatile release, in a temporal relationship similar to that observed during hot flushes. These authors independently suggest a possible opioid etiology for menopausal flushes. Thus, the bulk of evidence appears to favour central noradrenergic instability as the initiating mechanism of flush episodes occasioned by the reduction of endogenous opioid activity. Increased opioid activity appears to inhibit noradrenergic activity as well as flushes, and decreased opioid activity favours increased noradrenergic activity and the occurrence of flushes. The activation of CRF-POMC system during flush episodes may be related to stress. We look forward to further research on the neuroendocrine basis for menopausal flushes, which may confirm or refute this hypothesis.

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